

move substantially from the coating even at elevated temperatures. Iron, in contrast, which is 74% of 316L stainless steel, will not flow through gold at room temperature but can diffuse completely through a 7- μ m gold layer with 100-second exposure to a temperature that will raise its diffusivity to 10^{-8} cm²/s. We did observe enhanced iron diffusion into the heated gold coating (although it was not sufficient to reach the surface), virtually no impurities in the coating, and no difference in the surface gold elemental content of baked and unheated gold-plated stents.

Nonetheless, even limited metal diffusion can have significant mechanical advantages. Elemental diffusion creates a tighter bond between the gold coat and underlying stainless steel that minimizes the mechanical trauma from buckling or cracking with differential expansion. These theoretical effects, coupled with our data, suggest that if gold coatings are to be applied to stents, they should undergo some type of thermal processing.

Recoil, Intimal Hyperplasia, and Luminal Stenosis

Coatings by necessity changes strut thickness and expansion dynamics. The latter may become especially problematic when stent and coating metals are of different material strengths. Standard coating techniques increase strut thicknesses by twice the coating depth and strengthen devices against expansion and recoil. If the thickness is kept constant but some of the original metal is replaced with a softer substitute, there will be less resistance to expansion and recoil. When the thrombotic, inflammatory, and proliferative responses to the metal coating combine with recoil, there is a complementary effect on luminal integrity. A metal that elicits a greater vascular response but resists recoil to a greater extent than control stents may in fact produce a greater luminal diameter. This was the case for the 16-mm stents used in the second set of studies whose coating was laid down on unmodified struts. In contrast, when there is enhanced recoil and a significant vascular response, luminal diameter may be decreased even more than anticipated. That we did not observe the expected lower recoil of gold-coated stents in study 4 likely reflects the difficulty in making these measurements in an animal model system at the terminus of the experiments. Further work in metallurgy and material science will enable independent optimization of stent coatings and strength.

Conclusions

Coated, plated, and surface-modified stents are the devices of the future. Analysis of their reactivity is complex and multifactorial, including interdependence of surface and bulk properties of the materials and composite devices. There is a tradeoff between radiopacity and the dynamics of stent expansion, recoil, and intimal hyperplasia. In a 21st century version of the alchemist's dream, postplating processing can turn "plain gold" into "better gold," reducing inflammatory and intimal hyperplastic reactions.

Quo ferrea primum desinet ac toto surget gens aurea mundo [The age of iron comes to an end. In every region of the world the golden race appears anew.]
P. Vergili Maronis. *Ecloga Quarta*, 8–10.

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Stent Design: Implications for Restenosis

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There is increasing evidence that stent design influences angiographic restenosis and clinical outcomes. After nearly 15 years of clinical experience, there is now a plethora of stent designs available, and yet no single design incorporates all the characteristics of the ideal stent. The specific metallic composition of a stent limits the type of stent geometry possible, and the biocompatibility of the metal or surface coating may affect long-term stent healing. Studies have shown that stent geometry designed to optimize expansion and lower recoil is a prerequisite for favorable clinical outcomes. Strut thickness appears to be an important risk factor for restenosis, but changing one parameter, such as strut thickness, requires altering other design characteristics, thus altering the overall stent design. Future stent designs should combine the best features of conventional stent design with special modifications to facilitate multi-agent drug elution for a variety of applications.











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With more than 80% utilization, “stentomania” has been driven by gratifying acute procedural success and by results extrapolated from observational and randomized trials showing reduced restenosis and clinical events compared to other coronary interventional procedures. There is increasing evidence that stent design influences angiographic restenosis and clinical outcomes. Although restenosis-limiting drug-eluting stents are on the regulatory approval horizon, their projected high cost may not justify immediate widespread use in light of somewhat less-than-perfect clinical benefits, as recently reported in the Paclitaxel-Eluting NIR stent for the Treatment of In-Stent

Table 1
Comparison of Selected Stent Designs

Stent		Manufacturing method	Strut thickness	Geometry
Cordis Palmaz-Schatz ^a		Laser cut 316L SS tube	0.0025"	Spiral articulated slotted tube design
Cordis Crown ^a		Laser cut 316L SS tube	0.0027"	Sinusoidal pattern
Bx Velocity ^b		Laser cut 316L SS tube	0.0055"	Curved sections and interconnected N-links
S670 ^c		Laser cut 316L SS tube welded together	0.005" to 0.006"	Helically fused sinusoidal elements
S7 ^c		Laser cut 316L SS tube welded together	0.004" to 0.005"	Sinusoidal ring with elliptical-rectangular design
ACS MULTI-LINK ^d		Laser cut 316L SS tube	0.0022"	Corrugated ring
MULTI-LINK ^e TETRA TM		Laser cut 316L SS tube	0.0036" to 0.0049"	3-3-3 Linked corrugated ring
MULTI-LINK ^e PENTA TM		Laser cut 316L SS tube	0.0036" to 0.0049"	Corrugated ring with curved access links
NIR ^f		Laser cut 316L SS sheet rolled and welded edge to edge	0.0037"	Closed cell, transformable geometry
Express TM		Laser cut 316L SS tube	0.0049"	Tandem architecture

^aCordis Corporation, Miami, FL

^bMedtronic, Inc., Minneapolis, MN

^cGuidant Corporation, Indianapolis, IN

^dBoston Scientific Corporation, Natick, MA

Restenosis (TAXUS III) trial¹ and the Sirolimus-Coated Bx Velocity Stent in Treatment of Patients with De-Novo Coronary Artery Lesions (SIRIUS) trial.² Before discarding bare-metal stents, it may be worthwhile to take another look at stent design with respect to target vessel failure.

Stent Engineering

The ideal stent possesses a low profile, good flexibility to navigate tortuous

vessels, adequate radiopacity, low recoil, sufficient radial strength, a low metal surface area, high scaffolding

design incorporates all the characteristics of the ideal stent. This review is limited to balloon-expandable

"Stentomania" has been driven by gratifying acute procedural success.

ability, and thrombo-resistivity. After nearly 15 years of clinical experience, there is now a plethora of stent designs available, and yet no single

metallic stents, which make up 99% of the implantable devices used in the treatment of coronary artery disease.

Table 1 classifies stents in common

usage according to manufacturing methods, metallurgy, and dimensional/geometric properties. Stents are manufactured by laser cutting patterns in metal tubing (Palmaz-Schatz, Bx Velocity™ [Cordis Corporation, Miami, FL], and MULTI-LINK®

has little impact on stent performance, as stents of similar geometry manufactured by different techniques appear to behave similarly.

Stent metallurgy has also been widely evaluated. Nearly all balloon-expandable stents in use today are

may allow the routine manufacture of thinner, more radiopaque stents that cause less distortion on a magnetic resonance imaging (MRI) scan. Thus it seems that the specific metallic composition of a stent has two ways to influence restenosis: the limits metallurgy imposes on mechanical properties affect the universe of stent geometries possible which impact on implantation injury, and the biocompatibility of the metal may affect long-term stent healing.

Stent geometry, dimensions such as length and thickness, and stent surface properties appear to highly influence both thrombosis and restenosis rates. Prior to combination antiplatelet therapy, a higher metal surface area was thought to facilitate thrombus formation. In a bid to reduce the percentage metal surface area and also to improve access to side branches, stents with larger or open cells were designed. Concern has been raised from intravascular ultrasound (IVUS) observations that this results in tissue prolapse, leading to more restenosis,⁴ but this has been difficult to demonstrate clinically. Conversely,

Stent geometry, dimensions such as length and thickness, and stent surface properties appear to highly influence both thrombosis and restenosis rates.

[Guidant Corporation, Indianapolis, IN]) or sheets that are subsequently rolled into cylinders whose edges are welded together (NIR® [Boston Scientific Corporation, Natick, MA]). Hybrid methods exist for welding together multiple links cut from tubing (S670, S7 [Medtronic, Inc., Indianapolis, IN], and others). These construction methods offer stents with excellent crush resistance, wall coverage, and low recoil, but they are intrinsically relatively inflexible, hence reducing deliverability through tortuous vessel. Deliverability can be altered by improving the trackability of the balloon delivery system, and flexibility is also affected by changes in metallurgy or by creating specific geometric structures within the stent that flex more easily in the axial dimension.

Older construction techniques of winding or weaving strands of solid wire (Gianturco-Roubin I and II [GR-II, Cook, Inc., Bloomington, IN], Wiktor™ [Medtronic, Inc.]) have been largely abandoned. These stents were very flexible, even on less trackable balloon systems, but they had poorer scaffolding ability and crush resistance and higher recoil, resulting in smaller minimal lumen diameters (MLDs) and higher restenosis rates. With the possible exception of wound or woven stents, the specific manufacturing method

made from the alloy 316L stainless steel. This alloy is relatively easy to work with, can be plastically deformed to large expansion ratios without yielding or fatiguing, has low intrinsic elastic recoil (2%–3%), and has a long history of hemocompatibility. Previous attempts to make stents from tantalum, martenitic nitinol, platinum, and titanium alloys have largely been abandoned because these materials have less acceptable mechanical properties; for example, nitinol has higher recoil (6%–10%), requiring oversizing to create the same MLD and thus resulting in more mechanical injury. Recently, concern has been raised over nickel leaching, which

No single design incorporates all the characteristics of the ideal stent.

results in chronic inflammation. Stainless steel has about 5% nickel content, but its surface is generally a passivated chromium oxide. Although the amount of nickel leached into the surrounding tissue is less than that caused by normal dietary intake, patients with a positive patch test for nickel allergy may be at increased risk for developing in-stent restenosis.³

Cobalt chromium alloys are currently being evaluated as a replacement for 316L stainless steel. This

conformability, or the degree that the expanded stent can bend on its long axis, is higher with the "open-cell" designs. This may be important, as longitudinal straightening of vessels after stent deployment has been associated with late ischemic events.⁵

Animal Studies

Evidence from animal models show that stent geometry and thickness can affect experimental vascular injury and neointimal proliferation.

Table 2
Stent Trials for Restenosis

	Trial stent	Control stent	No. Pts	Late loss index	Binary restenosis	Clinical events	Target lesion/vessel revascularization
Lansky ¹⁰	GR-II	PS	760	0.76 vs 0.57; $P < .01$	47.3 vs 20.6%; $P < .001$	29.8% vs 17.8%; $P < .001$	TLR: 27.4% vs 15.3%; $P < .001$
Baim ¹¹	MULTI-LINK*	PS	1040 (538 angio)	0.42 ± 0.08 vs 0.43 ± 0.09; $P = ns$	16.0% vs 22.1%; $P = ns$	15.1% vs 16.7%; $P = ns$	TLR: 7.7% vs 9.8%; TVR: 10.6% vs 11.5%
Baim ¹²	NIR*	PS	849 (298 angio)	0.48 ± 0.43 vs 0.56 ± 0.44; $P = ns$	19.3% vs 22.4%; $P = ns$	16.0% vs 17.2%; $P = ns$	TLR: 9.6% vs 11.6%; TVR: 12.2% vs 13.4%
Heuser ¹³	AVE Microstent*	PS	661	0.59 ± 0.36 vs 0.5 ± 0.45; $P = .1$	25.2% vs 22.1%; $P = ns$	17.3% vs 13.3%; $P = .16$	TLR: 13.0% vs 19.8%; $P = .21$
Kastrati ¹⁴	(MULTI-LINK*, Inflow [†] , NIR*, PS, PURA [‡]) anonymous order	1147	0.51 ± 0.38	25.3% 0.58 ± 0.46 0.54 ± 0.41 0.60 ± 0.43 0.57 ± 0.45	17.6% 35.0% 28.6% 35.9% 29.4%	14.0% 30.6% 21.0% 28.1% 21.1%	24.4% 15.4% 21.0% 15.0%
Kastrati ¹⁵	MULTI-LINK DUET™	MULTI-LINK*	651	1.17 ± 0.78 vs 0.94 ± 0.74 (late loss); $P < .001$	15% vs 25.8%; $P = .003$	20% vs 15%	13.8% vs 8.6%; $P = .03$
Schuhlen ¹⁶	Bx Velocity™	MULTI-LINK*	661	0.65 ± 0.44 vs 0.51 ± 0.37; $P < .001$	31.4% vs 17.9%; $P < .001$	28.2% vs 17.2%	21.9% vs 12.3%; $P = .002$
Kastrati ¹⁷	Gold-coated Inflow	Inflow	731	0.64 ± 0.39 vs 0.55 ± 0.39; $P < .003$	49% vs 38.1%; $P < .003$	62.9% vs 73.9%; $P = .001$	TVR: 26.0% vs 13.6%; $P < .001$
Silber ¹⁸	NIR* Royale	NIR* Primo	603	0.65 vs 0.45; $P < .001$	37.5% vs 20.6%; $P < .001$	23.6 vs 17.5%; $P = ns$	18.7% vs 13.8%; $P = ns$

PS, Palmaz-Schatz; GR-II, Gianturco-Roubin II; TLR, target lesion revascularization; TVR, target vessel revascularization.

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†Inflow Dynamics, Munich, Germany

‡Elder, Mumbai, India

In rabbit iliac arteries, corrugated-ring stents of the MULTI-LINK* design achieved the same initial lumen diameters but imposed a lower arterial injury score than slotted tube stents and resulted in less neointimal hyperplasia.⁶ Preclinical trials have also shown that post-deployment in-stent lumen geometry, as dictated by stent design, determined neointimal thickness independently of arterial injury.⁷ Corrugated-ring stents with 12 struts per cross-section

achieved a more circular lumen and had less mural thrombus and less neointimal area than slotted tube stents, with only 8 struts per cross-section and a more polygonal cross-section.

Stent surface characteristics may be relevant with respect to thrombosis and restenosis. Stainless steel stents are generally electropolished to a mirror-quality finish. Removal of microscopic roughness appears to decrease platelet adhesion when the

stent is exposed to flowing blood in in vitro extracorporeal shunt models.⁸ Gold and platinum plating have been applied to stainless steel stents to improve fluoroscopic visibility. Preclinical studies suggested that gold has lower thrombogenicity than standard surfaces.⁹

Clinical Studies

Table 2 compares clinical results in several stent-versus-stent clinical trials.¹⁰⁻¹⁸ Early on, many of these trials

were designed and statistically analyzed as equivalency studies versus the Palmaz-Schatz (PS) stent to obtain U.S. FDA regulatory approval. Only a few trials have been designed to determine if one stent design is superior to another. Even so, there has been adequate statistical power to see some differences in a few cases. The Cook GR-II coiled stent had higher 6-month angiographic and clinical restenosis rates than the PS stent. A limitation of this study

not shown superiority of the corrugated-ring stents with respect to angiographic or clinical indices, intravascular ultrasound-evaluated subsets showed that the Guidant MULTI-LINK® design has less tissue proliferation at 6 months than the PS control stent.⁴

Advances in stent design have increased the types of lesions that can be treated. Recent studies by the Intracoronary Stenting and Angiographic Results (ISAR) trial

More recently the ISAR STEREO II trial has shown that the original MULTI-LINK® stent has a 40% lower restenosis and target lesion revascularization rate than the Cordis Bx Velocity™ stent.

was that a large number of the GR-II stents were undersized and longer in length compared to the PS stents.¹⁰ This notwithstanding, this study indicates that stent geometry designed to optimize expansion and lower recoil is prerequisite for favorable clinical outcomes.

Trials were designed to show equivalency rather than superiority of emerging new stents compared to the PS stent in order to obtain approval from the Food and Drug Administration. Not surprisingly, these equivalency trials did not show the clear superiority of other stents over the PS stent for the prevention of restenosis or improvement of clinical outcomes. The stent equivalency studies were further limited because they did not represent real-world stenting. Patients in these studies generally had focal lesions in larger vessels. Patient selection required lesions thought to be suitable for PS stenting, with its bulky 5-French sheath delivery system; therefore, lesions with angulation, tortuosity, calcification, and thrombus were often excluded.

Although equivalency trials have

group indicate, however, that advantages associated with increased deliverability and acute lumen gain may be offset by higher restenosis rates because more difficult lesions are intrinsically at higher risk for restenosis. Thus, in an unselected population, and despite similar acute luminal gains, 6-month restenosis rates varied between 25.3%–35.9% for five stents with varying designs, with the lowest restenosis and best clinical outcomes seen with the

Thickness Effect on Restenosis Outcome (STEREO) I trial, the second-generation MULTI-LINK DUET™ stent, with increased strut thickness and more of an “open-celled” design, had significantly higher restenosis compared to the original thin-strut MULTI-LINK® stent.¹⁵ The authors concluded that thinner-walled stents have a restenosis advantage. More recently the ISAR STEREO II trial has shown that the original MULTI-LINK® stent has a 40% lower restenosis and target lesion revascularization rate than the Cordis Bx Velocity™ stent.¹⁶ Despite the differences in stent geometry, these authors concluded that strut thickness is an independent risk factor for restenosis. The major limitation of these studies is that changing one parameter such as strut thickness requires altering other design characteristics so that the stent remains balloon-expandable at reasonable balloon pressures.

Finally, clinical trials have now demonstrated worse angiographic restenosis in gold-plated stents versus the same stent with bare stainless steel surfaces.^{17,18} This has been postulated to be due to an exaggerated vascular response, impurities of the coating, incomplete coating

Chronic inflammation might also result from electrochemical forces on the surface of stent struts, which may also increase stent interactions with circulating proteins.

multi-link design.¹⁴ Criticism of this study was that it did not control specifically for similar lesion types between the analyzed stents and that the study was performed at only two centers by the same group of investigators.

To increase radiopacity, many of the newer-generation stents have been designed with increased strut thickness. In the ISAR: Strut

resulting in roughening of stent surface, and increased strut thickness due to gold coating. Chronic inflammation might also result from electrochemical forces on the surface of stent struts, which may also increase stent interactions with circulating proteins.

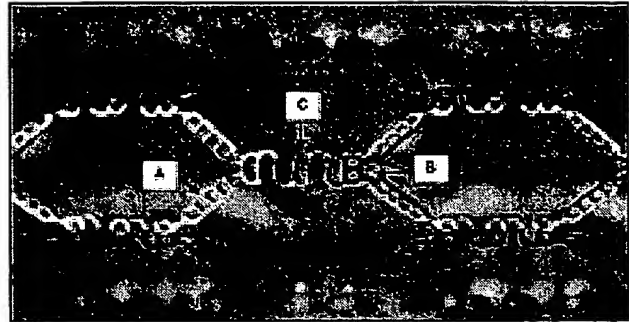
Taken as a whole, these data tell us that a variety of design parameters, including cell geometry, strut thick-

ness, acute recoil, and surface characteristics, have an important effect on clinical outcomes. Stents with the best combination of parameters consistently have angiographic restenosis rates in the 15%–18% range and target lesion revascularization in 7%–14% range, depending on the severity of clinical cohort. It will be difficult to do substantially better by design or surface characteristics alone without the addition of specific local pharmacological intervention.

The Future

The incidence of in-stent restenosis in easier-to-treat coronary lesions has been reduced using first-generation drug-eluting stents. Successful devices have utilized conventional “pre-drug-eluting” metallic stent designs coated with thin (5–10 μ) elastomeric biostable polymer surface membrane coatings. As such, first-generation drug-eluting stents may also have several limitations, such as late incidence of stent malposition to vessel wall and dehiscence or deformation of the polymer during expansion to large diameters. Moreover, the Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization (RAVEL) trial¹⁹ and early reports from the SIRIUS trial,² each comparing the sirolimus-eluting Bx VelocityTM stent with the same stent without drug/polymer, only confirm that the BX VelocityTM

Figure 1. Conor stent metallic backbone: (A) strut with laser-drilled holes for polymer/drug wells; (B) ductile hinges; (C) sinusoidal bridge with drug/polymer wells.



bare-metal stent has an intrinsically high restenosis rate in the 27%–32% range. One can only wonder what the results would have been if the control stent had been one with consistently lower restenosis. Although it is likely that a drug-eluting stent would be superior, the margin of difference could have been substantially lower, and a cost-versus-benefit analysis might yield results more favorable to the conventional stent.

As one example of a second-generation drug-eluting stent, the Conor Medsystems (Palo Alto, CA) stent (Figure 1) is specifically designed for programmable drug delivery to the vessel wall for restenosis and, simultaneously or separately, to deliver drugs or biological macromolecules to the lumen for treating indications beyond restenosis, such as diffuse disease or vulnerable plaque, or to deliver angiogenic or myogenic factors (Figure 2).

The unique design features of the

Conor stent include cored out or “honeycombed” strut elements linked to flexible sinusoidal bridges by specially contoured features called “ductile hinges.” Conventional stent designs are said to be prismatic structures because they consist of repeating units where the entire structure is deformed by expansion forces placed on it. The Conor stent differs in that all significant deformation is confined to the 10% of the stent comprised of the ductile hinges, rendering the struts and bridges as passive elements. This effectively decouples strut geometry from the mechanical properties of the stent. Expansion force, crush resistance, and elastic recoil are determined by the hinge design only. For example, wider or thicker struts can be added for greater radiopacity without affecting the mechanical properties of the stent, or alternatively, struts can be cored out with holes with no appreciable effect on the strength of the strut. Highly automated manufacturing

Main Points

- Evidence from animal models show that stent geometry and thickness can affect experimental vascular injury and neointimal proliferation.
- Stent equivalency trials are limited because they do not represent the “real world” of stenting.
- Aspects of stent design such as geometry, strut thickness, and surface characteristics have an important effect on angiographic restenosis and clinical outcome.
- Future stent designs aim to combine the best features of conventional stent design with special modifications to facilitate multi-agent chemotherapy for a variety of applications.

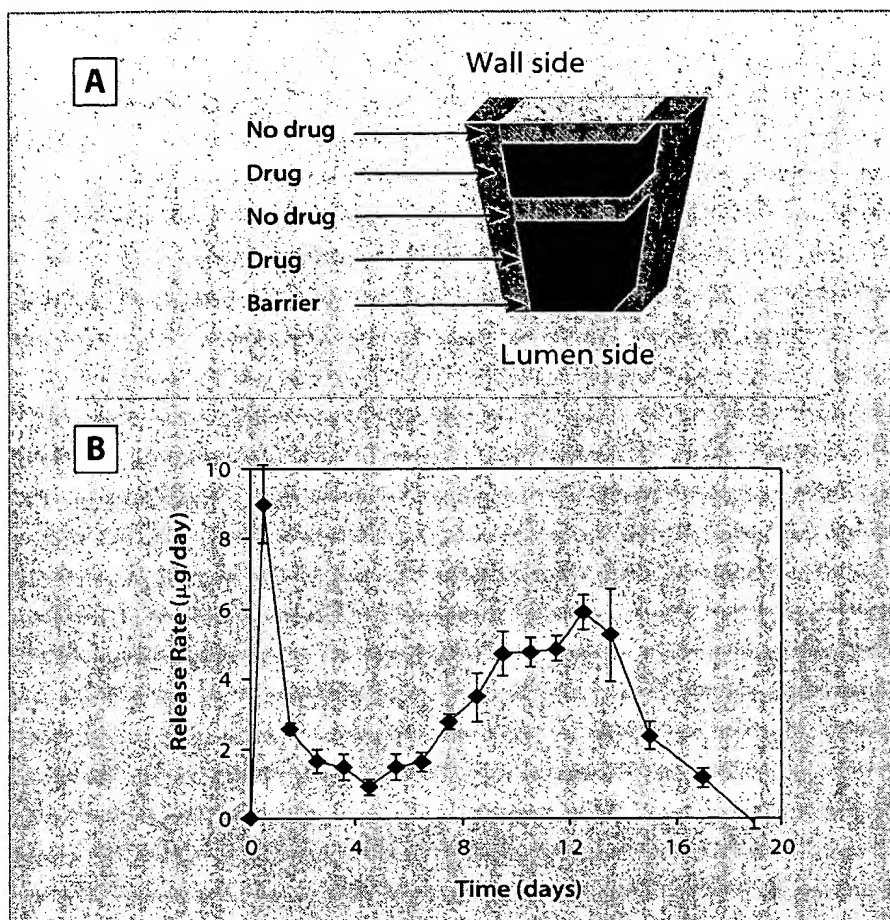


Figure 2. (A) Schematic of a programmable bioerodable polymer/drug well. The wall side has an empty layer of polymer to delay initial burst release. A middle layer is devoid of drug to elicit two peaks of drug release, and the lumen side has a slower degrading barrier layer so that drug flow is vectorially directed toward the wall side; (B) actual in vitro release kinetic profile of stent containing wells as in A, where the drug released is paclitaxel.

techniques permit programmable loading of individual holes with multiple layers of drug/polymer combinations. Thus, a given stent can contain a spatially distributed variation in the stacking of inlaid polymer/drug layers to achieve desired therapeutic goals. It is therefore likely that future stent design will combine the best features of conventional stents with special modifications to facilitate multi-agent chemotherapy for a variety of application. ■

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